Cell Metabolism
Previews

TXNIP Switches Tracks toward a Terminal UPR

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http://dx.doi.org/10.1016/j.cmet.2012.07.012

During the progression of diabetes, crosstalk between ER stress and inflammation controls islet cell fate. In this issue, Lerner et al. (2012) and Oslowski et al. (2012) discover that thioredoxin-interacting protein (TXNIP) is a regulatory switch connecting the terminal unfolded protein response (UPR) and NLRP3 inflammasome to mediate β cell death.

Excessive or protracted inflammation triggered by a chronic accumulation of metabolic factors is a hallmark of many degenerative diseases, including both type 1 and type 2 diabetes. Inflammation is the first means by which the immune system limits cell injury and damage in response to environmental irritants, pathogens, and infectious agents. Yet left unchecked, the inflammatory process turns toward cellular destruction and pyroptosis, a form of programmed cell death dependent on caspase-1 activation and proinflammatory cytokines. How the inflammatory process switches from stress remediation toward death pathways is a mystery. Recently, efforts directed at mechanisms linking metabolic overload with self-destruction and diabetes progression have discovered that uncontrolled endoplasmic reticulum (ER) stress is associated with a sterile but lethal inflammatory response (Hummasti and Hotamisligil, 2010). The molecular connection between these two biological responses, now identified in this issue, is thioredoxin-interacting protein (TXNIP) (Lerner et al., 2012; Oslowski et al., 2012).

Oxidative stress disrupts ER homeostasis, activating a multifaceted signaling program called the unfolded protein response (UPR). Three transmembrane sensors, namely inositol-requiring enzyme 1 (IRE1), PKR-like ER-resident kinase (PERK), and activating transcription factor 6 (ATF6) together elicit a program of gene expression designed to alleviate a build-up of misfolded proteins and regain ER homeostasis. Hyperactivation of the UPR to irremediable ER stress leads to inflammation and cell death, and in the case of the β cell, culminates in diabetes. In the current articles (Lerner et al., 2012; Oslowski et al., 2012), two of the three UPR sensors, namely IRE1α and PERK, play critical roles in regulating the expression of TXNIP. Treatment with pharmacologic agents that cause ER stress increased TXNIP mRNA levels in wild-type and *ATF6*$^{-/-}$ mouse embryonic fibroblasts but not in cells deficient for *IRE1α* or *PERK* (Lerner et al., 2012; Oslowski et al., 2012). Similarly, siRNA-mediated knockdown of *IRE1α* or *PERK*, but not *ATF6*, in insulinoma cells precluded TXNIP mRNA expression following ER stress (Oslowski et al., 2012). The lack of ATF6 involvement in regulating TXNIP expression emphasizes that the relationship between ER stress and inflammation occurs independent of the tripartite UPR. These findings are significant in that each sensor can have distinct functions implementing the UPR, with IRE1α and PERK each participating in cell destruction during unabated stress.

Urano and colleagues (Oslowski et al., 2012) then went further to identify the PERK-regulated transcription factors controlling TXNIP expression. During ER stress, PERK phosphorylates eukaryotic initiation factor 2 (eIF2), reducing global translation. This action lowers the influx of proteins into the ER and directs energy toward preferentially translating select mRNAs, such as ATF4, which promotes the expression of genes controlling redox status plus facilitates induction of the other arms of the UPR (Teske et al., 2011). However, following a screen of transcription factors regulated by PERK, it was concluded that ATF4 was not a significant regulator of TXNIP synthesis. Rather, a related transcription factor called ATF5, also subject to translational control by eIF2 phosphorylation, was shown via chromatin immunoprecipitation analysis to bind the *TNXIP* promoter during ER stress. These data demonstrate that the PERK arm of the UPR functions primarily to increase TXNIP transcription during ER stress.

The contribution of IRE1α in the regulation of TXNIP expression depends on its dual functions as both a protein kinase and an endoribonuclease. Upon remediable ER stress, IRE1α kinase domain is autophosphorylated, restricting its carboxy-terminal ribonuclease activity toward the mRNA encoding XBP-1 (X-box-binding protein 1). This splicing event produces a potent transcription factor that is important for triggering adaptive functions such as ER-to-Golgi protein transport, protein folding, and ER-associated degradation (ERAD) of misfolded proteins. Under conditions of irremediable ER stress, IRE1α ribonuclease activity becomes less discriminate (Han et al., 2009), and as described in this issue (Lerner et al., 2012), triggers decay of mi-R17, a regulator of TXNIP mRNA stability. Under normal conditions, TXNIP mRNA half-life is short, but during ER stress it becomes stabilized. Increased mRNA stability alone can lead to elevated mRNA expression, but when combined with PERK-mediated increase in transcription, a steeper induction results (Figure 1). This finding extends previous work by this group and others (Han et al., 2009; Hollien et al., 2009) by showing how IRE1α-dependent decay of mi-R17 tailors the transcriptome to ER stress. To validate these concepts in vivo, islets from the "Akita" mouse (Ins2$^{WT/C96Y}$), a model of diabetes caused by proinsulin misfolding, demonstrated reduced mi-R17 and elevated TXNIP mRNA. Furthermore,

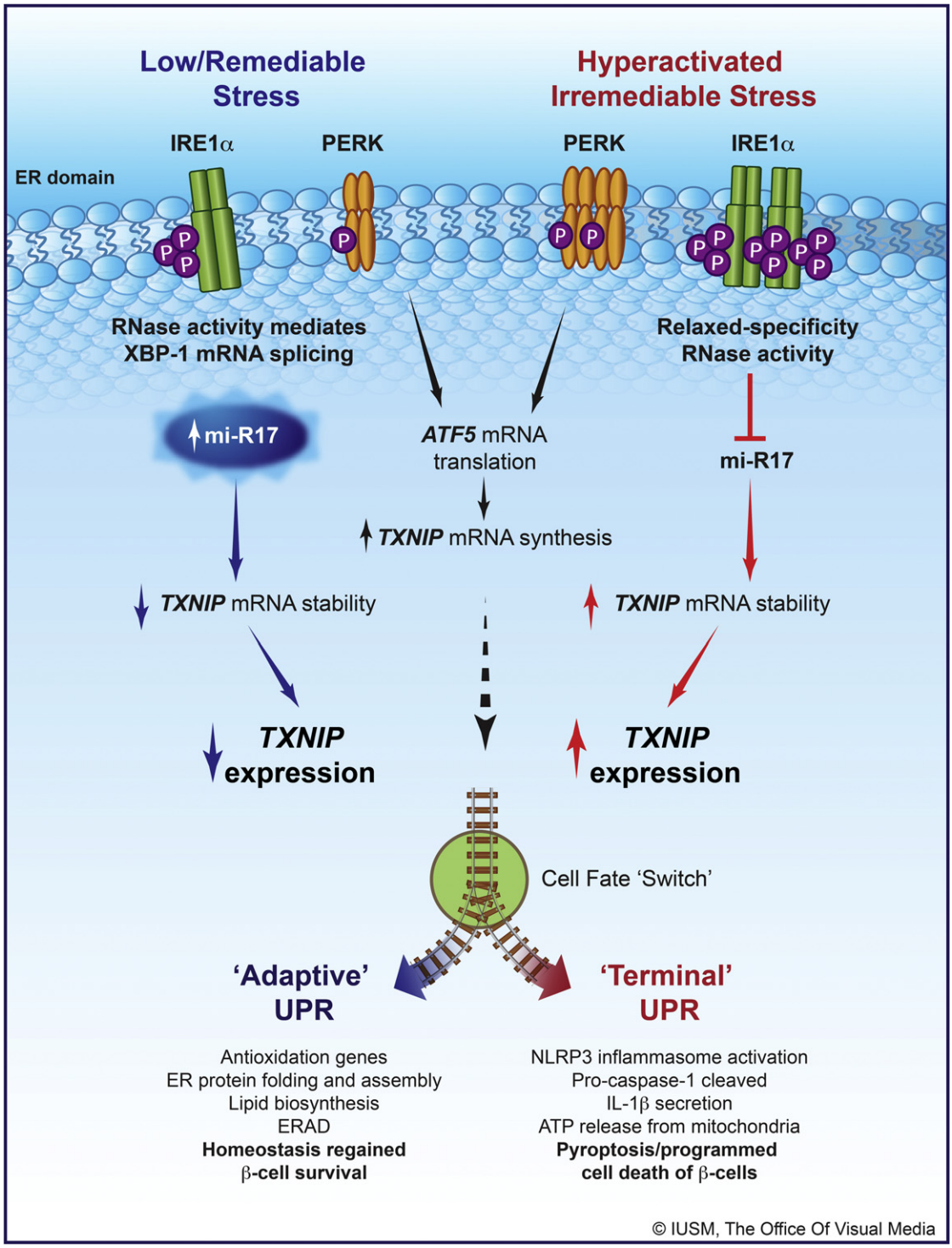

Figure 1. TXNIP Serves as the Wye Switch that Redirects β Cell Cell Fate from an Adaptive to Terminal UPR
β cells can encounter physiological conditions leading to low remediable ER stress (blue) or hyperactivated ER stress that is irremediable (red). These stress signals are recognized by ER-resident proteins IRE1α and PERK, which signal elevated expression of TXNIP. Elevated TXNIP levels during hyperactivated stress directs the wye switch for cell fate, leading to a terminal UPR, featuring activation of the inflammasome and pyroptosis.

pancreatic islets from *TXNIP*$^{-/-}$ mice showed reduced cell death in response to ER stress agents and genetic deletion of *TXNIP* in Akita mice protected them from hyperglycemia (Lerner et al., 2012). This study reveals that regulated mRNA stability of *TXNIP* contributes importantly to cell fate decisions during ER stress.

Chronic excess of metabolic factors (e.g., glucose, lipids) promotes formation of large, multiprotein complexes called inflammasomes. NOD-like receptor (NLR) proteins are key components of inflammasomes, facilitating caspase-1 maturation and secretion of cytokines in response to cellular danger (Schroder et al., 2010; Vandanmagsar et al., 2011). The NLRP3 inflammasome in particular functions as a sensor of metabolic stress activated by high glucose and reactive oxygen species (ROS) (Zhou et al., 2010). Thanks to the current studies (Lerner et al., 2012; Oslowski et al., 2012), the relationship between ER stress and the inflammasome is now clarified. With increased levels of TXNIP, the antioxidant function of thioredoxins are dampened, further increasing ROS, and binding of TXNIP to NLRP3 is promoted, activating caspase-1 cleavage, interleukin (IL)-1β secretion and pyroptosis. In support of this, inducing TXNIP expression increased caspase-3 cleavage and cell death in insulinoma cells, and pretreating human primary islets with IL-1 receptor antagonist reduced IL-1β and IL-6 expression and caspase-3/-7 activity to ER stress agents (Oslowski et al., 2012). TXNIP is therefore suggested to serve as a wye switch that can redirect the cell-fate railway track from an adaptive outcome to a terminal UPR (Figure 1).

Human conditions such as Wolfram syndrome type 1 ascribe loss of β cells to unmitigated ER stress and activation of the UPR. Significant levels of ER stress in β cells can also be the consequence of continued exposure to free fatty acids and cytokines (Hummasti and Hotamisligil, 2010). By identifying a novel path in the pathogenesis of diabetes, the current studies are foundational to the development of new treatment approaches. Importantly, Lerner et al. (2012) show that a drug that inhibits IRE1α endoribonuclease activity without affecting its kinase activity (STF-083010) reduces TXNIP expression and inflammasome activation in β cells. It is hopeful that this or other novel small-molecule inhibitors of this pathway can be tailored toward the treatment of diabetes and/or other degenerative diseases.

REFERENCES

Han, D., Lerner, A.G., Vande Walle, L., Upton, J.P., Xu, W., Hagen, A., Backes, B.J., Oakes, S.A., and Papa, F.R. (2009). Cell *138*, 562–575.

Hollien, J., Lin, J.H., Li, H., Stevens, N., Walter, P., and Weissman, J.S. (2009). J. Cell Biol. *186*, 323–331.

Hummasti, S., and Hotamisligil, G.S. (2010). Circ. Res. *107*, 579–591.

Lerner, A.G., Upton, J.-P., Praveen, P.V.K., Ghosh, R., Nakagawa, Y., Shen, S., Nguyen, V., Backes, B.J., Heiman, M., Heintz, N., et al. (2012). Cell Metab. *18*, this issue, 250–264.

Oslowski, C.M., Hara, T., O'Sullivan-Murphy, B., Kanekura, K., Lu, S., Hara, M., Ishigaki, S., Zhu, L.J., Hayashi, E., Hui, S.T., et al. (2012). Cell Metab. *18*, this issue, 265–273.

Schroder, K., Zhou, R., and Tschopp, J. (2010). Science *327*, 296–300.

Teske, B.F., Wek, S.A., Bunpo, P., Cundiff, J.K., McClintick, J.N., Anthony, T.G., and Wek, R.C. (2011). Mol. Biol. Cell *22*, 4390–4405.

Vandanmagsar, B., Youm, Y.H., Ravussin, A., Galgani, J.E., Stadler, K., Mynatt, R.L., Ravussin, E., Stephens, J.M., and Dixit, V.D. (2011). Nat. Med. *17*, 179–188.

Zhou, R., Tardivel, A., Thorens, B., Choi, I., and Tschopp, J. (2010). Nat. Immunol. *11*, 136–140.

Nutropioids, Hedonism in the Gut?

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http://dx.doi.org/10.1016/j.cmet.2012.07.011

The opioid system plays a pivotal role in how our brain regulates hedonic components of ingestive behavior. Duraffourd et al. (2012) add the gut to this opioid landscape, demonstrating direct activation of periportal μ-opioid receptors by food-derived opioid peptides (nutropioids), and a gut-brain feedback spiral that culminates in enhanced satiety.

For centuries, everybody—from chocolate lovers to steak aficionado—has agreed on the addictive reward of certain foods. In fact, "food cravings" have been shown to override even the strongest homeostatic drive. Their neuroanatomical and molecular underpinnings suggest striking similarities with central opioidergic mechanisms previously identified to mediate classic drug addictions. Accordingly, opioid receptors in the brain have been shown to orchestrate multiple hedonic components of ingestive behavior. An elegant study recently published in *Cell* now also introduces the gut as a potential control center for opioid response circuits regulating food intake (Duraffourd et al., 2012).

Opioid control of food intake has been studied for several decades. Endogenous opioid peptides such as endorphins were first identified in 1975 (Hughes, 1975). Today, the current model suggests that opioid signaling, especially via the μ-opioid receptor (MOR), is a major driver of both the "wanting" (i.e., incentive motivation and appetite) and "liking" (i.e., pleasure and palatability) aspects of ingestive behavior. "Nutropioids," i.e., opioid oligopeptides derived from food,